Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary health care: a randomised controlled trial

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Summary

Background Inappropriate antibiotic use for acute respiratory tract infections is common in primary health care, but distinguishing serious from self-limiting infections is difficult, particularly in low-resource settings. We assessed whether C-reactive protein point-of-care testing can safely reduce antibiotic use in patients with non-severe acute respiratory tract infections in Vietnam.

Method We did a multicentre open-label randomised controlled trial in ten primary health-care centres in northern Vietnam. Patients aged 1–65 years with at least one focal and one systemic symptom of acute respiratory tract infection were assigned 1:1 to receive either C-reactive protein point-of-care testing or routine care, following which antibiotic prescribing decisions were made. Patients with severe acute respiratory tract infection were excluded. Enrolled patients were reassessed on day 3, 4, or 5, and on day 14 a structured telephone interview was done blind to the intervention. Randomised assignments were concealed from prescribers and patients but not masked as the test result was used to assist treatment decisions. The primary outcome was antibiotic use within 14 days of follow-up. All analyses were prespecified in the protocol and the statistical analysis plan. All analyses were done on the intention-to-treat population and the analysis of the primary endpoint was repeated in the per-protocol population. This trial is registered under number NCT01918579.

Findings Between March 17, 2014, and July 3, 2015, 2037 patients (1028 children and 1009 adults) were enrolled and randomised. One adult patient withdrew immediately after randomisation. 1017 patients were assigned to receive C-reactive protein point-of-care testing, and 1019 patients were assigned to receive routine care. 115 patients in the C-reactive protein point-of-care group and 72 patients in the routine care group were excluded in the intention-to-treat analysis due to missing primary endpoint. The number of patients who used antibiotics within 14 days was 581 (64%) of 902 patients in the C-reactive protein group versus 738 (78%) of 947 patients in the control group (odds ratio [OR] 0·49, 95% CI 0·40–0·61; p<0·0001). Highly significant differences were seen in both children and adults, with substantial heterogeneity of the intervention effect across the 10 sites (I^2=84%, 95% CI 66–96). 140 patients in the C-reactive protein group and 137 patients in the routine care group missed the urine test on day 3, 4, or 5. Antibiotic activity in urine on day 3, 4, or 5 was found in 267 (30%) of 877 patients in the C-reactive protein group versus 314 (36%) of 882 patients in the routine treatment group (OR 0·78, 95% CI 0·63–0·95; p=0·015). Time to resolution of symptoms was similar in both groups. Adverse events were rare, with no deaths and a total of 14 hospital admissions (six in the C-reactive protein group and eight in the control group).

Interpretation C-reactive protein point-of-care testing reduced antibiotic use for non-severe acute respiratory tract infection without compromising patients' recovery in primary health care in Vietnam. Health-care providers might have become familiar with the clinical picture of low C-reactive protein, leading to reduction in antibiotic prescribing in both groups, but this would have led to a reduction in observed effect, rather than overestimation. Qualitative analysis is needed to address differences in context in order to implement this strategy to improve rational antibiotic use for patients with acute respiratory infection in low-income and middle-income countries.

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Introduction

Worldwide, bacterial pathogens are becoming increasingly resistant to antibiotics. This problem is particularly pressing in developing countries, where the burden of infectious disease is high and availability of newer, more expensive antibiotics is low.[1]

Vietnam already has a lot of antibiotic resistance. Prevalence of penicillin resistance is 71% and erythromycin resistance is 92% for *Streptococcus pneumoniae* in Vietnam, the highest in Asia.[2] Carbapenem resistance is high in *Pseudomonas aeruginosa* (25%) and *Acinetobacter baumannii* (40%) hospital-acquired

Research in context

Evidence before this study

In a 2014 Cochrane review, Aabenhus and Jensen searched several electronic database including CENTRAL, MEDLINE, Embase, CINAHL, Web of Science, and LILACS up to January, 2014, and identified six trials (three were individual randomised controlled trials [RCTs] and three were cluster RCTs). They found that cluster RCTs of C-reactive protein (CRP) testing was mostly effective in reducing antibiotic prescription. We searched MEDLINE and the Cochrane Library for articles published with the combination of "antibiotic", "primary care", "intervention", "respiratory tract infection", "C reactive protein" and "point-of-care". We found no recent trials in addition to those already included in the Cochrane review.

Added value of this study

All previous individual RCTs and cluster RCTs were done in European countries. No similar trial has been done in the primary health-care setting of low-income or middle-income countries, or for children. In the lower-middle-income country setting of Vietnam we assessed whether an affordable and practical C-reactive protein point-of-care test can aid in reducing antibiotic use safely in both adult and children with non-severe acute respiratory infections.

Implications of all the available evidence

Our findings indicate that the intervention could be applied in the resource-constrained settings of low-income and middle-income countries to improve rational antibiotic use for both children and adults with non-severe acute respiratory tract infection without compromising patients' recovery and satisfaction. Considerable heterogeneity between the ten health-care stations indicates the importance of regular review of any intervention and tailoring it to specific local context.

infections.[3] Development of resistance is multifactorial but a major driver is likely to be the frequent and often injudicious use of antibiotics in people and widespread use in agriculture and aquaculture.[4] In Vietnam, most antibiotics are purchased in private pharmacies without a prescription (88% in urban regions and 91% in rural regions), mostly for cough.[5]

In the community setting, most inappropriate antibiotics are prescribed or dispensed for acute respiratory tract infections, which are often self-limiting, in primary health centres or pharmacies.[6,7] Although data concerning the drivers of prescribing in primary health care in Vietnam are scarce, one of the main reasons identified is diagnostic uncertainty.[8] Distinguishing serious from self-limiting acute respiratory tract infection is challenging, and typically relies solely upon careful history and examination. Concerns of missing a serious infection can precipitate antibiotic prescription. In low-income settings, where health infrastructure is less developed, physicians might also be concerned about patients' perceived or actual inability to access health care if their condition deteriorates. These factors can motivate overuse of antibiotics. Implementation of a rapid, affordable point-of-care test to aid diagnosis and management and reduce antibiotic use safely is therefore an attractive prospect.

C-reactive protein (CRP) is a biomarker for the presence of an inflammatory process.[9,10] Several studies in high-income countries have shown that primary health-care providers who used a point-of-care CRP test prescribed fewer antibiotics in patients with cough, without adversely affecting patient recovery.[11,12] No such trials have been done in the primary health-care setting of low-income and middle-income countries where unrestricted antimicrobial access and antibiotic resistance is highest, and different social and clinical factors might affect its impact. Given the large number of self-limiting acute respiratory tract infections that present to primary care in Vietnam, even modest reductions would greatly decrease the absolute number of antibiotic prescriptions and thus one of the major drivers for bacterial resistance. Children in particular are frequently prescribed inappropriate antibiotics for acute respiratory tract infection, and any study should also address this important group.[7]

This study set out to assess the efficacy of CRP point-of-care testing for both children and adults presenting with non-severe acute respiratory tract infections at primary health-care centres in Vietnam to reduce inappropriate antibiotic use safely.

Methods

Study design

We did an open-label randomised controlled trial in ten selected primary health-care centres in northern Vietnam. Patients presenting with non-severe acute respiratory tract infection were randomly assigned to either CRP point-of-care testing (intervention) or routine care (control). Randomised assignments were concealed from prescribers and patients but not masked as the test result was used to assist treatment decisions.

Public health services in Vietnam are decentralised from nation to province, district and commune level. Primary health care (at the district and commune level) provides routine and urgent health care and hospital referral to the population. We aimed to include ten urban and rural primary health-care centres with a caseload of at least five acute respiratory tract infection cases per day within a 60 km radius of Hanoi. For urban centres, we invited all 20 existing regional polyclinics to participate; three did not respond, two refused to participate, and six did not meet the caseload criteria. Therefore we selected the remaining nine urban sites to implement the trial. For rural sites, we selected the outpatient clinics of one district general hospital (Ba Vi hospital), situated 60 km west of Hanoi. Caseloads of other non-hospital clinics in rural Hanoi were too low.

Patients

Patients aged 1–65 years who were visiting one of these primary health-care centres, and who were suspected of having non-severe acute respiratory tract infection with at least one focal and one systemic sign or symptom by the treating physician were eligible for this study. Focal signs and symptoms were cough, rhinitis, pharyngitis, shortness of breath, wheezing, chest pain, and auscultation abnormalities. Systemic signs and symptoms were fever, perspiration, headache, myalgia, and feeling generally unwell. Children were defined as patients aged 1–15 years. Patients with signs of severe acute respiratory tract infection were excluded. Detailed general and specific inclusion and exclusion criteria for adults and children are listed in the appendix.

A study doctor or study nurse explained to patients or legal guardians about the trial, including risks and benefits. After verbal agreement, written informed consent was obtained. Once consent was obtained, a case report form was completed for each patient containing all the information related to the study variables. All patients received a routine medical history and examination, consisting of medical history, mental status (Glasgow Coma Scale), vital signs (blood pressure, pulse, respiratory rate), and temperature. Further examinations were done at the discretion of the treating physician.

Randomisation and masking

Eligible patients were randomly assigned 1:1 to CRP point-of-care testing or control (routine care) using an individual randomisation method, stratified by health station and age category (child versus adult). The randomisation list was computer-generated using variable block lengths of four (with probability 0·75) and six (with probability 0·25). Allocation was concealed by opaque sealed envelopes,[13] opened at randomisation in strict chronological sequence. To protect the patient's identity, each participant was allocated a study identification number, which was used for all study material. Patients and investigators were not masked to treatment assignment, except for the conductors of the 2-week telephone interview, who were blinded to the intervention received by the interviewee.

Procedures

For patients in the intervention group, a finger prick to obtain capillary blood was done and analysed using the quantitative NycoCard analyser (CRP single test kit used with the NycoCard II Reader, Alere Technologies, Norway) on enrolment (day 0) and retested on day 3, 4, or 5. Patients in the control group were treated according to routine practice and local treatment guidelines on enrolment and the second visit. All patients were followed up at 2 weeks after the initial health clinic visit by a structured telephone interview.

Physicians were trained to use specific CRP cutoffs, which were based on previous studies and adapted for use in children.[12,14–16] We did a central initial training workshop, followed by further training during onsite implementation visits at the ten health centres by the study team. Training followed a model developed for a similar study in Maastricht, Netherlands, contextualised to the Vietnamese setting and carried out in Vietnamese.[15,17] Training materials were both verbal and written, consisting of oral presentations and written information leaflets for the doctors and health centres to keep for future reference. The health centres and doctors were given a telephone number to contact should any queries arise during the study. Laminated posters and desk reminders with recommended cutoff values for the specific age groups were provided.

See Online for appendix

The cutoffs used to recommend that antibiotics not be prescribed were a CRP of 20 mg/L or less for patients aged 6–65 years, and a CRP of 10 mg/L or less for patients aged 1–5 years. Doctors were advised that adults with a CRP of 100 mg/L or more and children with a CRP of 50 mg/L or more should generally receive antibiotics and hospital referral should be considered. Between these thresholds no specific recommendation was given and clinicians were advised to use their clinical discretion.

After 2 weeks, enrolled patients were interviewed via telephone, by interviewers blinded to the intervention, to assess whether they had been to any health clinic, whether they had taken any medication for the same acute respiratory tract infection, the source of any medication, any serious adverse events (eg, admission to hospital), time to resolution of acute respiratory tract infection symptoms, and satisfaction with the care provided. The patients were given a symptom diary as a memory aid on day 0.

Doctors requested the patients return to the clinic on day 3, 4, or 5. Urine samples from enrolled patients (except those lost to follow-up, toddlers who could not urinate on command at the visit, and women when menstruating) were collected by the original clinician on the second visit (day 3, 4, or 5) for testing for the presence of antimicrobials. Pansensitive ATCC 25923 *Staphylococcus aureus* and ATCC 25922 *Escherichia coli* on Müller Hinton agar (Oxoid) were cultured in the presence of the participant's urine.[18,19] We used a positive control from a patient who was on antibiotic treatment at the time of urine collection. Negative control urines were from healthy people who had not taken any drug for at least 3 days before urine collection. A positive result was a zone of clearing larger than 10 mm diameter in either or both agar plates with the two ATCC bacterial strains. The sensitivity of this test is reportedly 97·37%, and the specificity is around 98·85%.[19]

Outcomes

The primary endpoint was the number of patients receiving any antibiotic within 2 weeks of enrolment. Antibiotic use was defined as at least one of: antibiotic prescription at enrolment (day 0), antibiotic use reported at follow-up visit (day 3, 4, or 5), antibiotic prescription at second visit (day 3, 4, or 5), antimicrobial activity in urine, or antibiotic use reported at follow-up interview (day 14). Participants were classified as positive for antibiotic use if at least one of these conditions were met, negative if all five criteria were documented as negative, and missing if all reported criteria were negative but data were missing for at least one criterion.

Secondary endpoints were antimicrobial activity in urine (day 3, 4, or 5), the proportion of patients with immediate antibiotic prescription at enrolment, any antibiotic usage in patients without immediate prescription (subsequent antibiotic use or intervention failure), and prescriptions on the second visit in patients without an immediate antibiotic prescription (clinical management changed based on follow-up assessment). Additional secondary endpoints were the source of any antibiotic taken but not prescribed at enrolment or day 4 (self-medication, drug seller, doctor, or other), the frequency of reconsultations, serious adverse events (hospital admission or death), time to resolution of symptoms, and reported patient satisfaction with participating in the trial on day 14 (measured on a scale from 0 to 10). Patients with satisfaction score of 5 or more were considered satisfied.

For the **protocol** see https://clinicaltrials.gov/ct2/show/NCT01918579

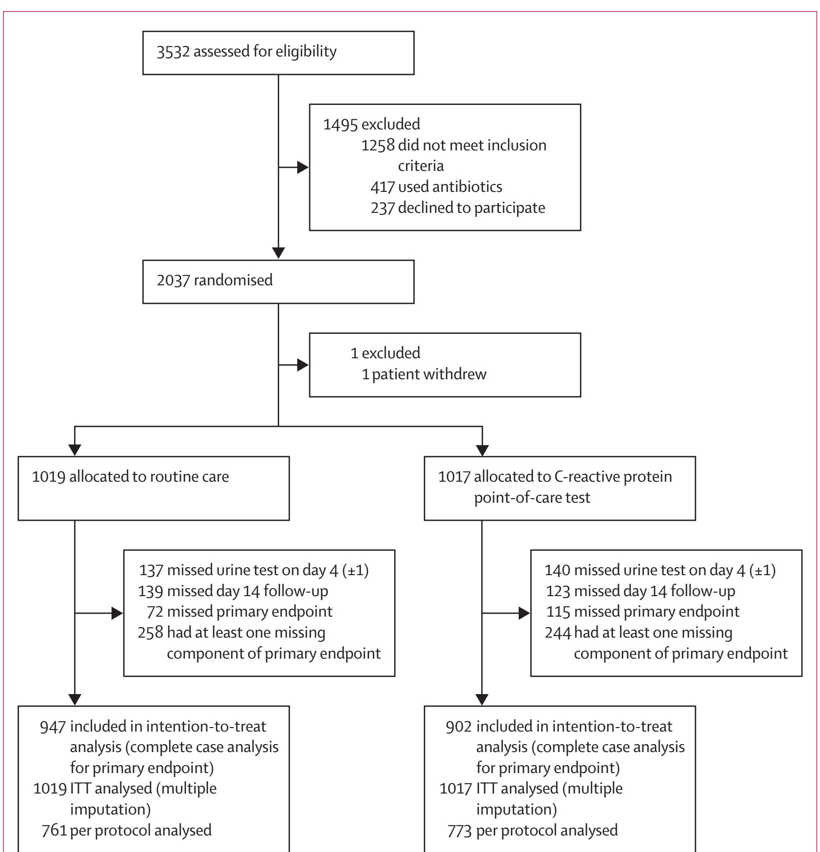

Figure 1: **Trial profile**

Excluded patients: 244 were younger than 1 year or older than 65 years; 16 had severe respiratory infection; one was referred to hospital; three had suspected tuberculosis; six had liver disease; 110 had a medical history of neoplastic disease, congestive cardiac failure, chronic obstructive pulmonary disease, insulin-dependent diabetes, or renal disease; 46 were pregnant; nine had no access to a telephone; 417 had already taken antibiotics; 65 had symptoms present for more than 2 weeks; 169 were not able to come for the follow-up visit; 237 declined to participate; 172 had no reason for exclusion recorded. ITT=intention-to-treat.

Statistical analysis

We expected CRP guidance to reduce antibiotic prescription for acute respiratory tract infection by at least 20%: from 80%[7] to 60%. However, increased awareness of the issue through the study could itself bring antibiotic prescription down, reducing the effect of CRP testing. Therefore, the trial was powered to detect a reduction of the antibiotic prescription rate from 70% to 60%, based on antibiotic use data from communities in Vietnam.[7] To detect such a difference with 90% power and two-sided 5% significance, a total of 477 patients were required per arm. To analyse adults and children separately, the target sample size was set at 2000 patients (50% children and 50% adults).

Statistical analyses were predefined in the protocol and the statistical analysis plan. The main population for all analyses was the intention-to-treat population including all randomised patients except for those who withdrew immediately, and analysis was according to the treatment arm. Patients with missing outcomes were excluded from the analysis. However, for the primary outcome, we also did an additional, alternative analysis based on multiple imputation of outcomes for those patients. Moreover, the analysis of the primary endpoint was repeated in the per-protocol population that included only patients for whom all components of the primary endpoint as mentioned above were non-missing.

For formal comparison of the composite primary endpoint and its components between the two treatment groups, we used a logistic regression model of the outcome depending on the treatment group and the age stratum (children *vs* adults) as fixed effects and the health-care centre as a random effect, thereby taking clustering within centres into account. Because we saw considerable heterogeneity in the primary endpoint between health-care centres, we decided post hoc to visualise results by site using forest plots and to do a standard random effects meta-analysis.

Time to resolution of symptoms was visualised using Kaplan-Meier curves and formal comparisons between the two treatment groups were based on the Cox proportional hazards model with the treatment assignment and the age stratum as fixed effects and the health-care centre as a Gaussian random effect (frailty). All data derivations were done with SAS version 9.2 (SAS Institute Inc, Cary, USA) and statistical analyses were done with the statistical software R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

The trial was approved by the ethics committees of the National Hospital for Tropical Diseases in Hanoi (39/IRB-NHTD) and the Oxford University Tropical Research Ethics Committee (OxTREC Reference: 176-12). Permission for this study was also obtained from local authorities. This trial is registered at ClinicalTrials.gov under number NCT01918579.

Role of the funding source

The funders of the study and Alere Technologies (who supplied reagents) had no role in the study design, data collection, data analysis and interpretation, or writing and submission of the study manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the manuscript submission for publication.

Results

Patients were enrolled from March 17, 2014, to July 3, 2015. Of 3532 patients screened, 1258 did not fulfil inclusion criteria, including 417 patients (33%) who had already taken antibiotics at presentation, and 237 who declined to participate. A total of 2037 patients from 10 centres (153–271 patients per site) were enrolled and randomised. One patient immediately withdrew after randomisation. 1017 patients (510 children, 507 adults) were randomly assigned to the CRP group and 1019 patients (518 children, 501 adults) were assigned to the control group. 115 (11%) of 1017 patients in the CRP group and 72 (7%) of 1019 patients in the control group did not have a primary outcome. The per-protocol analysis contained 773 patients in the CRP group and 761 in the control group (figure 1).

Characteristics of participants at enrolment were similar between both groups regarding age, duration of illness, vital signs, and clinical symptoms at presentation. 1224 (60%) of 2036 patients were female. Symptoms at presentation were: cough, sore throat, coryza, fever, dyspnoea, and earache (table 1).

In the intention-to-treat analysis, 581 (64%) of 902 patients in the CRP-guided group and 738 (78%) of 947 routine care patients used an antibiotic within 14 days of follow-up (odds ratio [OR] 0·49, 95% CI 0·40–0·61; p<0·0001). The corresponding effect sizes for the intention-to-treat analysis based on multiple imputation (0·50, 0·41–0·61; p<0·0001) and the per-protocol analysis (0·51, 0·41–0·63; p<0·0001) were similar and significant reductions were observed in both adults and children (table 2). There was substantial heterogeneity between the health centres (I^2=84%, 95% CI 66–96) and the pooled median treatment effect estimate (OR 0·47) from the random treatment effects model showed therefore a much wider 95% CI of 0·26–0·83 (figure 2).

In the intention-to-treat analysis, immediate antibiotic prescription at presentation was higher in the routine group (647 [63%] of 1019 patients) than in the CRP group (441 [43%] of 1017 patients; OR 0·41, 95% CI 0·34–0·49; p<0·0001). This difference was also significant in the per-protocol analysis (OR 0·46, 95% CI 0·37–0·57; p<0·0001). Significantly higher antibiotic prescription at presentation in the routine care group was seen in both children and adults (table 3).

Substantial heterogeneity in immediate antibiotic use between the health centres was detected (I^2=94%, 95% CI 87–98) (appendix). Subsequent antibiotic use without

	CRP (n=1017)	Control (n=1019)
Number of females	633 (62%)	591 (58%)
Age (years)	16 (8–39)	15 (8–41)
<6	141 (14%)	146 (14%)
6–15	369 (36%)	372 (37%)
>15	507 (50%)	501 (49%)
Duration of illness (days)	3 (2–3)	2 (2–3)
Vital signs		
Heart rate (beats/min)	80 (75–86)	80 (75–86)
Respiratory rate (breaths/min)	20 (19–23)	20 (19–23)
Systolic blood pressure* (mm Hg)	110 (100–120)	110 (100–120)
Diastolic blood pressure* (mm Hg)	70 (60–80)	70 (70–80)
Clinical symptoms		
Cough	891 (88%)	905 (89%)
Sore throat	830 (82%)	833 (82%)
Sputum	653 (64%)	638 (63%)
Coryza	632 (62%)	619 (61%)
Fever	364 (36%)	347 (34%)
Earache	48 (5%)	40 (4%)
Dyspnoea	23 (2%)	32 (3%)
Wheeze	40 (4%)	22 (2%)

Data are median (IQR) or number (%). *Blood pressure is reported for adults only. Age, sex, and heart rate were available for all patients and blood pressure was measured in all adults. Respiratory rate was missing for four (0·2%) patients, and clinical symptoms were missing for 13 (0·6%) of patients.

***Table 1*: Baseline characteristics**

	CRP	Control	OR (95% CI)	p value
Intention to treat; complete case analysis*	581/902 (64·4%)	738/947 (77·9%)	0·49 (0·40–0·61)	<0·0001
Intention to treat; multiple imputation analysis†	598/1017 (58·8%)	747/1019 (73·3%)	0·50 (0·41–0·61)	<0·0001
Per protocol analysis	452/773 (58·5%)	552/761 (72·5%)	0·51 (0·41–0·63)	<0·0001
Children (1–15 years)	295/448 (65·8%)	374/487 (76·8%)	0·55 (0·41–0·75)	0·0001
Adults (>15 years)	286/454 (63·0%)	364/460 (79·1%)	0·41 (0·30–0·56)	<0·0001

Data are events/n (%) unless otherwise specified. OR=odds ratio from logistic regression model adjusted for age group and random site effect. *Variance of random site effect was estimated as 0·41 implying an intra-class correlation of $0{\cdot}41/(0{\cdot}41+\pi^2)=0{\cdot}11$. An additive binomial regression model for the primary outcome (adjusted for age group and site effect) gives an adjusted absolute risk difference of –12·5% (95% CI –16·6 to –8·6), p<0·0001. †Based on 20 imputed datasets. Reported event numbers and proportions refer to averages across all imputed datasets.

***Table 2*: Patients receiving any antibiotics within 14 days of follow-up**

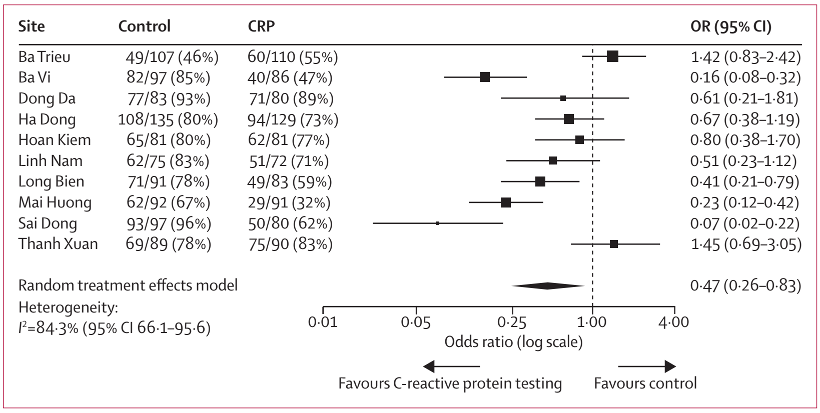

Figure 2: **Effect of C-reactive protein testing on evidence of antibiotic use during 14 days of follow-up, by centre**

	CRP	Control	OR (95% CI)	p value
Immediate antibiotic prescription				
All patients	441/1017 (43·4%)	647/1019 (63·5%)	0·41 (0·34–0·49)	<0·0001
Children	227/510 (44·5%)	333/518 (64·3%)	0·39 (0·30–0·52)	<0·0001
Adults	214/507 (42·2%)	314/501 (62·7%)	0·40 (0·30–0·52)	<0·0001
Subsequent antibiotic use*				
All patients	140/461 (30·4%)	91/300 (30·3%)	0·97 (0·70–1·35)	0·85
Children	68/221 (30·8%)	41/154 (26·6%)	1·22 (0·78–1·94)	0·38
Adults	72/240 (30·0%)	50/146 (34·2%)	0·73 (0·45–1·17)	0·19
Antibiotic management change*				
All patients	30/510 (5·9%)	12/345 (3·5%)	1·70 (0·85–3·41)	0·13
Children	8/255 (3·1%)	4/170 (2·4%)	1·09 (0·31–3·85)	0·89
Adults	22/255 (8·6%)	8/175 (4·6%)	1·99 (0·86–4·64)	0·11
Presence of antibiotics in urine				
All patients	267/877 (30·4%)	314/882 (35·6%)	0·78 (0·63–0·95)	0·015
Children	132/439 (30·1%)	159/448 (35·5%)	0·76 (0·56–1·01)	0·06
Adults	135/438 (30·8%)	155/434 (35·7%)	0·79 (0·59–1·06)	0·12
Time to resolution of symptoms (days)				
All patients	5 (4–7)	5 (4–7)	0·92 (0·84–1·02)‡	0·12
Children	5 (3–7)	5 (4–7)	0·97 (0·84–1·11)‡	0·64
Adults	6 (4–10)	5 (4–8)	0·89 (0·77–1·03)‡	0·10
Hospital admissions	6/901 (1%)	8/874 (1%)	..	0·60
Reconsultation	5/1017 (0·5%)	3/1019 (0·3%)	..	0·51
Satisfaction score†	9·00 (8·00–10·00)	9·00 (8·00–10·00)	..	0·75
Number of patients satisfied (satisfaction score 5 or more)	545/549 (99·3%)	541/542 (99·8%)	..	0·50

Data are events/n (%) or median (IQR). OR=odds ratio from logistic regression model adjusted for age group and random site effect. Comparisons based on logistic regression, Cox regression, Fisher's exact test (hospital admissions, reconsultation, and number of patients satisfied), or Wilcoxon rank sum test (satisfaction score). *Subsequent antibiotic and antibiotic management change are reported in patients without immediate antibiotic prescription only—ie, they refer to non-randomised comparisons because the denominator population depends on the treatment group. †Satisfaction score was measured on a scale from 0 to 10 and was only available in 549 patients in the C-reactive protein group and 542 patients in the control group. ‡Hazard ratio from Cox regression model adjusted for age group and random site effect.

Table 3: **Summary of secondary endpoints (intention-to-treat analysis)**

immediate prescription (intervention failure) within 14 days of follow-up was similar between the two groups at 140 (30%) of 461 patients in the CRP group and 91 (30%) 300 of patients in the routine care group (OR 0·97, 95% CI 0·7–1·35; p=0·85). The corresponding effect size was similar in children and adults (table 3). Among 165 patients (72 in the routine care group, 93 in the CRP group) who were using antibiotics without prescription at enrolment or the second visit, the source of antibiotics was recorded in 133 cases. The most frequent source was drug-seller-guided antibiotic use (66) followed by doctor's prescription (39) and self-medication (27), or other sources (1).

Antimicrobial activity in a urine sample on day 3, 4, or 5 was significantly lower in the CRP group than in the routine treatment group. In the intention-to-treat population, this was detected in 267 (30%) of 877 patients in the CRP group versus 314 (36%) of 882 patients in the routine treatment group (OR 0·78, 95% CI 0·63–0·95; p=0·015) (table 3). Antimicrobial activity was detected in 444 (47%) of 953 patients receiving immediate antibiotics. The agreement between recorded previous antibiotic use and detection of antimicrobial activity in the urine sample was moderate, with κ=0·43 (95% CI 0·39–0·47). In patients without recorded previous antibiotic use, 46 (9%) of 487 patients in the CRP group and 26 (8%) of 319 patients in the control group had a positive urine test. The number of positive urine tests in patients with recorded previous antibiotic use was 221 (57%) of 390 patients in the CRP group and 288 (51%) of 563 of patients in the routine care group. The number of positive urine tests in patients with recorded previous antibiotic use was lowest in the control group of the rural Ba Vi site, with 23 (32%) of 71 patients with a positive urine test. In patients who did not receive immediate antibiotic prescriptions, the number of patients with a prescription of an antibiotic on day 3, 4, or 5 (antibiotic management change) was 30 (6%) of 510 patients in the CRP group versus 12 (3%) 345 patients in the routine group in the intention-to-treat analysis (OR 1·70, 95% CI 0·85–3·41; p=0·13) (table 3).

Time to resolution of symptoms was similar between groups (figure 3), with a median duration of 5 days (IQR 4–7) in both groups (hazard ratio [HR] 0·92, 95% CI 0·84–1·02) (table 3). Adverse events, defined as hospital admission or death between enrolment and day 14, were rare, with zero deaths and 14 hospital admissions (eight in the routine treatment group and six in CRP group). Three of 1019 patients in the routine group and five of 1017 patients in CRP group needed reconsultation (table 3). We detected no differences in patients' satisfaction between randomised groups (table 3).

758 (75%) of 1017 CRP measurements in patients with immediate antibiotic prescription were less than 10 mg/L, 133 (13%) were 11–20 mg/L, 101 (10%) were 21–50 mg/L, and only 25 (2%) were more than 50 mg/L. For children younger than 6 years, 28 (35%) of 81 patients

received immediate antibiotic prescription when the CRP value at enrolment was 10 mg/L or less. 171 (37%) of 459 adults received immediate antibiotic prescription when the CRP value at day 0 was 20 mg/L or less (appendix). Adherence to the intervention algorithm was highly variable across sites. For patients aged 6–65 years with a CRP value at day 0 of 20 mg/L or less, the immediate antibiotic prescription rate ranged from three (4%) of 75 patients (in Sai Dong station) to 49 (71%) of 69 patients (in Dong Da station).

Discussion

This study shows that access to CRP point-of-care testing reduces unnecessary antibiotic use for non-severe acute respiratory infections in adults and children in primary health care in Vietnam, without compromising clinical recovery or serious adverse events. Our findings were consistent across all outcome measures we used: dispensing and prescribing data, patient self-report, and microbiologically confirmed antibiotic presence in urine. This trial is the first to investigate the effects of CRP point-of-care testing in a resource-constrained setting and the impact of CRP testing on antibiotic use in children has never been assessed before in a randomised controlled trial.

With an overall absolute reduction of 14% (78% *vs* 64%) in antibiotic use, the effect of CRP testing in our trial is similar to that reported in the Netherlands, where the reduction was 12% (65% *vs* 53%; risk ratio [RR] 0·81)[20] and higher than in Norway, where a non-significant reduction was seen (RR 0·95, 95% CI 0·76–1·18).[21] Cluster-randomised controlled trials in the Netherlands and Russia showed significant reductions of 18%[15] and 15%,[14] respectively. The decline in immediate prescription rate was also larger in our study than with previous individual randomised controlled trials[17,21,22] but lower than in cluster-randomised controlled trials.[12,14,15]

There was a high degree of heterogeneity in the effect of CRP point-of-care testing across sites. Several sites probably did not adhere to the intervention algorithm. The reasons why physicians did not follow the CRP algorithm are not known. A full qualitative assessment of the intervention was done and will be reported separately. Of note, the results of a previous study[12] in European countries suggests that an intervention combining CRP testing and education had the largest effect on prescribing.

Similar to results from previous trials, no differences regarding recovery, serious adverse events, and patients' satisfaction were seen after the introduction of CRP testing, although given the benign clinical syndrome addressed it was unlikely to be powered to detect differences in outcome. One trial has previously documented an increase in hospital admissions associated with CRP-guided treatment. However, this adverse event was rare (a total of 30 in 4264 patients) and concerns regarding this risk should be balanced against benefits of reducing inappropriate antibiotic use on a large scale.[12]

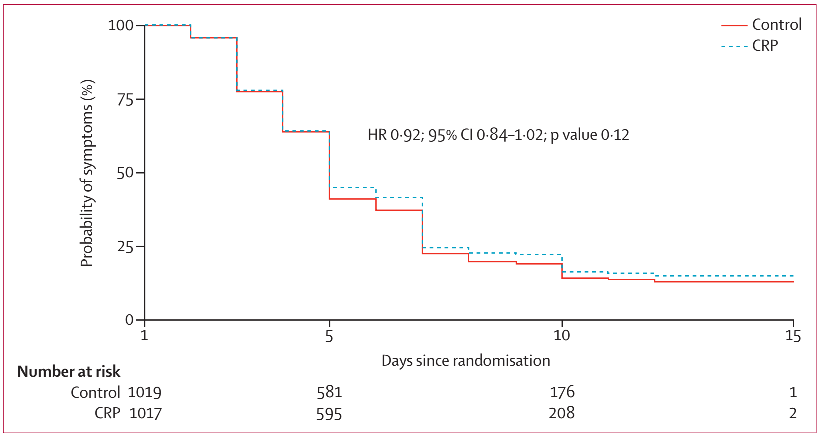

***Figure 3*: Kaplan-Meier curve of time to resolution of symptoms after enrolment by treatment arm**
CRP=C-reactive protein test. HR=hazard ratio.

Such adverse events were also exceedingly rare in our study with no apparent difference between the groups.

Although most previous large trials only looked at prescribing data or self-reporting on antibiotic usage, tests of urinary antimicrobial activity provided additional information in this study. In comparison to rates of immediate antibiotic prescription (43% in the CRP group *vs* 64% in the routine group), rates of detection of urine antimicrobial activity were substantially lower: 36% in the CRP group versus 30% in the routine group. The agreement between recorded antibiotic use and detection of antimicrobial activity in urine was only moderate (κ=0·43)[23] and detection of antimicrobial activity in urine was lower in the control group and lowest in the control group of the rural Ba Vi site. This might be explained by patients stopping their antibiotic treatment before the second visit on day 3, 4, or 5 as suggested by a previous study among children in rural Vietnam that reported that 341 (42%) of 818 patients used antibiotics for only 1 or 2 days.[24] A further explanation could be biliary excretion of several frequently prescribed antibiotics such as azithromycin or spiramycin.

Procalcitonin might be an alternative biomarker to CRP. Procalcitonin was shown to be an effective biomarker in reducing antibiotic use for acute respiratory tract infections in primary care setting in European countries.[25–27] However, no well validated point-of-care test for procalcitonin that is feasible for use in low-income settings is commercially available as far as we are aware. Furthermore, a 2015 study[28] assessed the diagnostic accuracy of procalcitonin and CRP in distinguishing common viral and bacterial infections three south Asian countries in which malaria is endemic. That study indicated that, when applied to samples from febrile patients with mono-infections, CRP was a highly sensitive and moderately specific biomarker for discriminating viral infections from bacterial infections (rickettsiosis/leptospirosis, bacteraemia), and from malaria. CRP had a higher sensitivity and specificity in discriminating viral and bacterial infections than procalcitonin in this study.

With the large sample size, our trial was robust to assess the intervention effect in different age subgroups in a real-life situation. This provides us with relevant data on what obstacles need to be overcome to make the intervention even more effective. Our findings suggest that CRP testing could be an important component of non-antibiotic management strategies for acute respiratory tract infection in primary care settings in low-income and middle-income countries. The intervention has the potential of being scaled up as several commercially affordable CRP rapid point-of-care tests have been assessed and seen to be reliable.[29] Before widely introducing CRP point-of-care tests as routine care, a cost-effectiveness analysis should be done to assess other additional requirements, including test cost, training, and consultation time, compared with the reduction in antibiotic prescription and subsequent burden of resistance. To achieve maximal impact on antibiotic consumption in settings, such as Vietnam, where antibiotic use is commonly off-prescription, further work investigating the potential for point-of-care CRP testing in pharmacies and drug stores will be needed. This trial provides important data necessary for planning such studies. There might be lessons to be learnt from the roll-out of rapid diagnostic tests in community settings.[30]

There are several limitations of our study. Over time, clinicians might have become familiar with the clinical picture associated with low CRP, resulting in reduced antibiotic prescriptions even in individuals randomly assigned to the control group. A cluster randomised controled trial design might have prevented this contamination effect but would be more costly. However, this limitation would have led to a reduction in the observed effect rather than an overestimation. We might not have captured all antibiotic use by the second visit, the diary, urine test, and the day 14 interview. Patients might not have reported antibiotic use due to poor recall or self-perceived misuse of antibiotics or were unaware that pills they were given were antibiotics. However, this bias should be equally distributed across groups. Lastly the heterogeneity of the effect is far from ideal, but is likely to represent differences in context that will be explored further in qualitative analyses and must be addressed for successful implementation of this strategy.

Antibiotic use for acute respiratory infections was significantly reduced by C-reactive protein guidance at the point of care. We saw a considerable heterogeneity between the ten health-care stations, providing important lessons for implementation. Our findings indicate that the intervention could be applied in the resource-constrained settings of low-income and middle-income countries to improve rational antibiotic use for patients with acute respiratory tract infection (adults and children) without compromising patients' recovery and satisfaction.

Contributors

HFLW was responsible for conception, study design, and funding application. All authors contributed to the study protocol development. NTTD and LBH led day-to-day management of the study implementation supervised by HFLW. NTDT, NTHT, and HMT took part in getting ethics approval and training for health-care centres. BTNV was responsible for laboratory work. MW led statistical data analysis. NTTD, DTVV, and MW had full access to the database and are responsible for data analysis accuracy. Drafting of manuscript was done by NTTD, BN, and HFLW. All authors contributed to the final revision and approved the submission.

Declaration of interests

We declare no competing interests.

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References

1 Alsan M, Schoemaker L, Eggleston K, Kammili N, Kolli P, Bhattacharya J. Out-of-pocket health expenditures and antimicrobial resistance in low-income and middle-income countries: an economic analysis. *Lancet Infect Dis* 2015; **15:** 1203–10.

2 Song JH, Jung SI, Ko KS, et al. High prevalence of antimicrobial resistance among clinical *Streptococcus pneumoniae* isolates in Asia (an ANSORP study). *Antimicrob Agents Chemother* 2004; **48:** 2101–07.

3 Nguyen KV, Thi Do NT, Chandna A, et al. Antibiotic use and resistance in emerging economies: a situation analysis for Viet Nam. *BMC Public Health* 2013; **13:** 1158.

4 World Health Organization's strategy to contain resistance to antimicrobial drugs. *Rev Panam Salud Publica* 2001; **10:** 284–94 (in Spanish).

5 Nga do TT, Chuc NT, Hoa NP, et al. Antibiotic sales in rural and urban pharmacies in northern Vietnam: an observational study. *BMC Pharmacol Toxicol* 2014; **15:** 6.

6 Larsson M, Falkenberg T, Dardashti A, et al. Overprescribing of antibiotics to children in rural Vietnam. *Scand J Infect Dis* 2005; **37:** 442–48.

7 Nguyen QH, Nguyen TK, Ho D, Larsson M, Eriksson B, Lundborg CS. Unnecessary antibiotic use for mild acute respiratory infections during 28-day follow-up of 823 children under five in rural Vietnam. *Trans R Soc Trop Med Hyg* 2011; **105:** 628–36.

8 Whaley LE, Businger AC, Dempsey PP, Linder JA. Visit complexity, diagnostic uncertainty, and antibiotic prescribing for acute cough in primary care: a retrospective study. *BMC Fam Pract* 2013; **14:** 120.

9 Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004; **39:** 206–17.

10 Lubell Y BS, Dunachie S, Tanganuchitcharnchai A, et al. Performance of C-reactive protein and procalcitonin to distinguish viral from bacterial and malarial causes of fever in Southeast Asia. *BMC Infect Dis* 2015; published online Nov 11. DOI:10.1186/s12879-015-1272-6.

11 Aabenhus R, Jensen JU, Jorgensen KJ, Hrobjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. *Cochrane Database Syst Rev* 2014; **11:** CD010130.

12 Little P, Stuart B, Francis N, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013; **382:** 1175–82.

13 Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care* 2005; **20:** 187–91.

14 Andreeva E, Melbye H. Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. *BMC Fam Pract* 2014; **15:** 80.

15 Cals JW, Butler CC, Hopstaken RM, Hood K, Dinant GJ. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009; **338:** b1374.

16 Segal I, Ehrlichman M, Urbach J, Bar-Meir M. Use of time from fever onset improves the diagnostic accuracy of C-reactive protein in identifying bacterial infections. *Arch Dis Child* 2014; **99:** 974–78.

17 Cals JW, Chappin FH, Hopstaken RM, et al. C-reactive protein point-of-care testing for lower respiratory tract infections: a qualitative evaluation of experiences by GPs. *Fam Pract* 2010; **27:** 212–18.

18 Liu YC, Huang WK, Huang TS, Kunin CM. Detection of antimicrobial activity in urine for epidemiologic studies of antibiotic use. *J Clin Epidemiol* 1999; **52:** 539–45.

19 Wilson G, Badarudeen S, Godwin A. Antibiotic screening of urine culture as a useful quality audit. *J Infect Dev Ctries* 2011; **5:** 299–302.

20 Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. *Ann Fam Med* 2010; **8:** 124–33.

21 Melbye H, Aaraas I, Fleten N, Kolstrup N, Mikalsen JI. The value of C-reactive protein testing in suspected lower respiratory tract infections. A study from general practice on the effect of a rapid test on antibiotic research and course of the disease in adults. *Tidsskr Nor Llaegeforen* 1995; **115:** 1610–15 (in Norwegian).

22 Diederichsen HZ, Skamling M, Diederichsen A, et al. Randomised controlled trial of CRP rapid test as a guide to treatment of respiratory infections in general practice. *Scand J Prim Health Care* 2000; **18:** 39–43.

23 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33:** 159–74.

24 Hoa NQ, Trung NV, Larsson M, et al. Decreased *Streptococcus pneumoniae* susceptibility to oral antibiotics among children in rural Vietnam: a community study. *BMC Infect Dis* 2010; **10**: 85.

25 Briel M, Schuetz P, Mueller B, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med* 2008; **168**: 2000–07.

26 Burkhardt O, Ewig S, Haagen U, et al. Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection. *Eur Respir J* 2010; **36:** 601–07.

27 Meili M, Kutz A, Briel M, et al. Infection biomarkers in primary care patients with acute respiratory tract infections—comparison of Procalcitonin and C-reactive protein. *BMC Pulm Med* 2016; **16:** 43.

28 Lubell Y, Blacksell SD, Dunachie S, et al. Performance of C-reactive protein and procalcitonin to distinguish viral from bacterial and malarial causes of fever in Southeast Asia. *BMC Infect Dis* 2015; **15:** 511.

29 Phommasone K, Althaus T, Souvanthong P, et al. Accuracy of commercially available c-reactive protein rapid tests in the context of undifferentiated fevers in rural Laos. *BMC Infect Dis* 2016; **16:** 61.

30 Bastiaens GJ, Bousema T, Leslie T. Scale-up of malaria rapid diagnostic tests and artemisinin-based combination therapy: challenges and perspectives in sub-Saharan Africa. *PLoS Med* 2014; **11:** e1001590.